Exhibit 18

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Benign gynecologic conditions are associated with ovarian cancer risk in African-American women: a case–control study

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Abstract

Background The association between common benign gynecologic conditions and ovarian cancer remains under-studied in African Americans. Therefore, we examine the association between self-reported history of benign gynecologic conditions and epithelial ovarian cancer risk in African-American women.

Methods Data from a large population-based, multi-center case–control study of epithelial ovarian cancer in African-American women were analyzed to estimate the association between self-reported history of endometriosis, pelvic inflammatory disease (PID), fibroid, and ovarian cyst with epithelial ovarian cancer. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between individual and composite gynecologic conditions and ovarian cancer.

Results 600 cases and 752 controls enrolled in the African American Cancer Epidemiology Study between 1 December 2010 and 31 December 2015 comprised the study population. After adjusting for potential confounders, a history of endometriosis was associated with ovarian cancer (OR 1.78; 95% CI 1.09–2.90). A non-significant association of similar magnitude was observed with PID (OR 1.33; 95% CI 0.82–2.16), while no association was observed in women with a history of fibroid or ovarian cyst. A positive trend was observed for an increasing number of reported gynecologic conditions ($p = 0.006$) with consistency across histologic subtypes and among both oral contraceptive users and non-users.

Conclusion A self-reported history of endometriosis among African-American women was associated with increased risk of ovarian cancer. Having multiple benign gynecologic conditions also increased ovarian cancer risk.

Keywords Ovarian cancer · African-American · Endometriosis · Pelvic inflammatory disease (PID) · Ovarian cyst · Uterine fibroid · African-American Cancer Epidemiology Study (AACES)

Abbreviations

PID	Pelvic inflammatory disease
OC	Oral contraceptive
AACES	African-American Cancer Epidemiology Study
SEER	Surveillance, Epidemiology, and End Results
AJCC	American Joint Committee on Cancer
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index

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Introduction

Accumulating epidemiologic evidence suggests that endometriosis is associated with approximately twofold increased risk of developing non-serous epithelial ovarian cancer [1–4]. Studying the pathophysiology and biologic risk factors associated with endometriosis has helped elucidate potential mechanisms of tumorigenesis in non-serous ovarian cancer subtypes distinct from that of serous carcinoma. Chronic inflammation, aberrant immune response, genetic alterations, and hormonal imbalance marked by excess estrogen have been implicated in the multi-step malignant transformation of benign endometriotic cells [5–8]. The epidemiologic linkage between endometriosis and ovarian cancer and the strength of the associations estimated from studies

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of predominantly white women remain to be confirmed in other race and ethnicities.

Other gynecologic conditions, such as pelvic inflammatory disease (PID) [9–11] and ovarian cyst [12], have been associated with increased risk of ovarian cancer in a small number of studies; however, findings are conflicting [4, 13–16]. The association between uterine fibroids, a condition which disproportionately affects African-American women [17, 18], and ovarian cancer is largely unknown. Any potential association observed between fibroids and ovarian cancer may be modified or confounded by increased rates of hysterectomy and procedure-related interruption of tubal patency and ovarian blood supply in women with fibroids [19–21]. Similarly, oral contraceptive (OC) is frequently prescribed as treatment for benign gynecologic conditions, and OC use could potentially alter the ovarian cancer risk associated with benign gynecologic conditions.

The link between these common benign gynecologic conditions and ovarian cancer remains under-studied in African-Americans. In this study, we explore the relationship between self-reported history of benign gynecologic conditions (endometriosis, PID, uterine fibroid, and ovarian cyst) and epithelial ovarian cancer in African-American women. While the exact biological etiologies remain to be fully elucidated, these gynecologic pathologies all affect a pro-inflammatory milieu. The association between having multiple gynecologic conditions and ovarian cancer was also examined to assess the potential effect of the increased burden of inflammation-related exposures.

Materials and methods

The data used in these analyses were collected as part of the African-American Cancer Epidemiology Study (AACES), a population-based, case–control study of ovarian cancer in African-American women from 11 geographic regions (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Study participants completed informed consent prior to enrollment in the study and institutional review board approval was obtained from all participating institutions. The methods of the study have been previously reported in detail [22], and a brief summary of the study methods follows.

Cases were identified through rapid case ascertainment systems using either state cancer registries, Surveillance, Epidemiology, and End Results (SEER) registries, or individual hospital registries. Inclusion criteria were as follows: self-identified African-American/Black race, age 20–79 years at diagnosis, pathology-confirmed invasive epithelial ovarian cancer diagnosis between 1 December 2010 and 31 December 2015, and ability to complete an interview in English. Controls were identified through random digit dialing and frequency matched to cases on 5-year age groups and geographic region. Controls were eligible if they had at least one intact ovary, self-identified as African-American/black race, and were 20–79 years at baseline interview. Accrual began in December 2010, and the current analyses include 600 cases and 752 controls enrolled in the study as of December 2017.

Participants were asked to complete a baseline interviewer-administered, computer-assisted telephone survey. Information collected included demographic characteristics; reproductive, gynecologic and medical history; hormone use; family history of cancer; and lifestyle characteristics such as smoking, alcohol consumption, and physical activity. In addition, participants were asked if they had ever been diagnosed with endometriosis, PID, uterine fibroid or ovarian cyst (yes/no). The interviewer provided a scripted description of the conditions if the participant was not familiar with the medical terminology. If a participant reported a history of these conditions, she was asked to provide the age at first diagnosis. In our analyses, participants who were diagnosed with any gynecologic condition 1 year or less before ovarian cancer diagnosis (cases) or interview date (controls) were coded as not having the condition to reduce surveillance bias. A sensitivity analysis (diagnosis of gynecologic condition 3, 5, or 10 years or less before ovarian cancer diagnosis or baseline interview coded as not having the condition) was performed to evaluate the length of time between diagnosis of gynecologic condition and the referent date (ovarian cancer diagnosis or baseline interview) and its association with ovarian cancer risk.

Overall, 8.7% of cases and 2.5% of controls completed a shorter version of the survey. All variables examined in our analysis were ascertained in both the long and short versions of the survey. Missing data for endometriosis (4 cases), fibroid (1 cases), PID (5 cases, 2 controls), and ovarian cyst (1 control) were conservatively coded as not having the condition. The distribution of demographic and descriptive characteristics, including frequency of reported gynecologic conditions, between cases and controls was compared using Student's t-test and Chi-square test for continuous and categorical/ordinal variables, respectively. For cases, the mean age at ovarian cancer diagnosis was compared among those with and without a history of each gynecologic condition using Student's *t* test. In addition, the distribution of histologic subtype and American Joint Committee on Cancer (AJCC) stage was summarized by gynecologic condition.

Logistic regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between history of endometriosis, PID, uterine fibroid or ovarian cyst and the risk of ovarian cancer. Known or potential confounders were selected a priori and included in the multivariable model as follows: reference age (age at

diagnosis for cases, age at baseline interview for controls) category (20–29, 30–49, 50–69, 70–79), geographic region (South/mid-Atlantic, South Central, Midwest), marital status (single/never married, married/living with partner, divorced/separated/widowed), education (high school or less, some post-high school training, college or graduate degree), body mass index (BMI in kg/m^2, continuous variable), parity (0, 1, 2, 3 or more), tubal ligation (yes/no), duration of OC use (never, <60 months, ≥ 60 months), first degree family history of breast or ovarian cancer (yes/no), talc use (never use, any genital use, non-genital use only), endometriosis (yes/no), PID (yes/no), fibroid (yes/no), and ovarian cyst (yes/no). An expanded regression model additionally included hysterectomy status (yes/no) to examine the potential confounding effect of hysterectomy. Hysterectomy status was limited to those performed more than 1 year before the ovarian cancer diagnosis or baseline interview to reduce detection bias.

To explore a potential dose–response relationship, multivariable logistic regression analyses were performed to calculate the association between the total number of benign conditions (0, 1, 2, or more) and risk of ovarian cancer. ORs are reported from categorical models and p values for trend are reported from continuous models to test for the linear trend related to an increasing number of benign conditions. The referent group was women with no history endometriosis, PID, fibroid, or ovarian cyst.

The association between the benign conditions and ovarian cancer risk was further examined in a stratified analysis by histologic subtype (serous/non-serous). Non-serous subtypes were further stratified into endometrioid, mucinous, clear cell, or other subtype in a supplemental analysis. In addition, the potential modifying effect of OC use on ovarian cancer risk associated with gynecologic conditions was evaluated in a stratified analysis by history of OC use (never use/ever use). The interaction between history of OC use and gynecologic conditions was assessed by including a multiplicative term in the models. All statistical analyses were performed using SAS version 9.3 (Cary, North Carolina).

Results

600 cases and 752 controls were included in the analysis. Comparison of demographic and clinical characteristics of cases and controls is presented in Table 1. Cases were older, less likely to be married or living with a partner, and less likely to have post-high school education compared to controls. Cases also were more likely to report having a first degree female relative with breast or ovarian cancer, former smoking, genital talc use, and nulliparity, compared to controls. Cases were less likely to report history of tubal ligation or OC use, but the proportion reporting hysterectomy was similar between the two groups. Cases were more likely to report endometriosis (8.2% vs. 4.4%, $p=0.004$) and PID (7.3% vs. 4.7%, $p=0.037$). There was no difference in the reporting of uterine fibroid (41.7% vs. 36.6%, $p=0.056$) and ovarian cyst between cases and controls (13.3% vs. 11.2%, $p=0.226$).

The association between benign gynecologic conditions and risk of epithelial ovarian cancer is shown in Table 2. A history of endometriosis was associated with ovarian cancer (OR 1.78; 95% CI 1.09–2.90) after adjusting for age, study site, marital status, education, BMI, parity, tubal ligation, duration of OC use, family history of breast or ovarian cancer, talc use, and history of PID, fibroid or ovarian cyst. The adjustment variables are all suggested risk factors for ovarian cancer and some are more common in the African American community. For example, talc use is highly prevalent in the African American community and excluding this variable over-estimated the associations in our analysis (data not shown).

An association was observed in women with a history of PID (OR 1.33; 95% CI 0.82–2.16), although the result did not reach statistical significance. While no association was observed in women with a history fibroid (OR 1.10; 95% CI 0.86–1.40) and ovarian cyst (OR 1.18; 95% CI 0.92–1.52), a positive trend of increasing OR was observed with increasing number of benign gynecologic conditions ($p=0.006$). For women who reported 2 or more gynecological conditions, 31% had PID, 37% had endometriosis, 64% had cysts, and 93% had fibroids. Direction and magnitude of associations remained essentially unchanged when hysterectomy status was included in the regression model or when the gynecologic diagnosis was censored at 3, 5, and 10 years from the referent date (data not shown).

The relationship between benign gynecologic conditions and epithelial ovarian cancer stratified by serous vs. non-serous histology is shown in Table 3. Endometriosis was associated with a near threefold increase in non-serous ovarian cancer (OR 2.80; 95% CI 1.53–5.10). Odds of serous ovarian cancer was also increased among women with a history of endometriosis, but the association was not significant (OR 1.29; 95% CI 0.71–2.35). Similarly, non-significant associations were observed for PID with both serous (OR 1.65; 95% CI 0.98–2.79) and non-serous (OR 0.90; 95% CI 0.42–1.91) ovarian cancer. No histologic subtype-specific association was observed with history of fibroid, or ovarian cyst. The risk of both serous and non-serous ovarian cancer increased with increasing number of benign gynecologic conditions. A history of 2 or more conditions was associated with a 1.5- to 2-fold increased risk of serous (OR 1.51; 95% CI 1.00–2.29) and non-serous ovarian cancer (OR 2.13; 95% CI 1.32–3.46). Further analysis of non-serous ovarian cancer stratified by histologic subtypes suggested positive associations between endometriosis

Table 1 Demographic and clinical characteristics of ovarian cancer cases and controls in the African American Cancer Epidemiology Study

Characteristics	Total $n=1,352$ (%)	Cases $n=600$ (%)	Control $n=752$ (%)	p value
Age (mean years, range)	56.3 (20–79)	58.1 (20–79)	55.0 (20–79)	<0.001
BMI (kg/m^2)	32.3 (14.8–78.3)	32.8 (14.8–74.4)	32.0 (15.9–78.3)	0.064
Marital status				0.001
Single, never married	328 (24.3)	144 (24.0)	184 (24.5)	
Married or living with partner	509 (37.6)	197 (32.8)	312 (41.5)	
Divorced/separated or widowed	515 (38.1)	259 (43.2)	256 (34.0)	
Education				0.021
High school or less	550 (40.7)	269 (44.8)	281 (37.4)	
Some post-high school training	358 (26.5)	147 (24.5)	211 (28.1)	
College or graduate degree	444 (32.8)	184 (30.7)	260 (34.6)	
Menstrual status				0.171
Pre/peri-menopause	386 (28.6)	160 (26.7)	226 (30.1)	
Menopause	966 (71.4)	440 (73.3)	526 (69.9)	
Medical history				
Pulmonary disease[a]	220 (16.3)	96 (16.0)	124 (16.5)	0.809
Diabetes	315 (2,336)	137 (22.8)	178 (23.7)	0.718
Cardiac disease[b]	147 (10.9)	64 (10.7)	83 (11.0)	0.828
Hypertension	829 (61.3)	403 (67.2)	426 (56.7)	<0.001
Anemia	451 (33.3)	236 (39.3)	215 (28.6)	<0.001
1st degree female relative with breast/ovarian cancer				<0.001
Yes	292 (21.6)	158 (26.3)	134 (17.8)	
No	1,060 (78.4)	442 (73.7)	618 (82.2)	
Cigarette smoking				<0.001
Never smoker	769 (56.9)	332 (55.3)	437 (58.1)	
Current smoker	209 (15.5)	61 (10.2)	148 (19.7)	
Former smoker	374 (27.7)	207 (34.5)	167 (22.2)	
Talc use				<0.001
Never use	578 (42.8)	224 (37.3)	354 (47.1)	
Any genital use	519 (38.4)	264 (44.0)	255 (33.9)	
Non-genital use only	255 (18.9)	112 (18.7)	143 (19.0)	
Parity (# of live births)				0.033
0	207 (15.3)	111 (18.5)	96 (12.8)	
1	251 (18.6)	108 (18.0)	143 (19.0)	
2	345 (25.5)	144 (24.0)	201 (26.7)	
3+	548 (40.6)	236 (39.4)	312 (41.5)	
Tubal ligation				0.060
Yes	513 (37.9)	211 (35.2)	302 (40.2)	
No	839 (62.1)	389 (64.8)	450 (59.8)	
OC use				<0.001
Never	346 (25.6)	188 (31.3)	158 (21.0)	
<60 months	574 (42.5)	237 (39.5)	337 (44.8)	
≥60 months	432 (32.0)	175 (29.2)	257 (34.2)	
Hysterectomy[c]				0.605
Yes	311 (23.0)	142 (23.7)	169 (22.5)	
No	1,041 (77.0)	458 (76.3)	583 (77.5)	
Benign gynecologic condition[d]				
Endometriosis	82 (6.1)	49 (8.2)	33 (4.4)	0.004
PID	79 (5.8)	44 (7.3)	35 (4.7)	0.037
Fibroid	525 (38.8)	250 (41.7)	275 (36.6)	0.056
Ovarian cyst	164 (12.1)	80 (13.3)	84 (11.2)	0.226

Table 1 (continued)

Characteristics	Total $n=1,352$ (%)	Cases $n=600$ (%)	Control $n=752$ (%)	p value
Histology				
High-grade serous		365 (60.8)		
Low-grade serous		17 (2.8)		
Endometrioid		56 (9.3)		
Clear cell		20 (3.3)		
Mucinous		31 (5.2)		
Carcinosarcoma		16 (2.7)		
Other[e]		75 (12.5)		
Missing		20 (3.3)		
Stage				
I/II		188 (31.3)		
III/IV		366 (61.0)		
Unknown		46 (7.7)		

Missing or unknown data: BMI (4 cases, 1 control), parity (1 case)

BMI body mass index, *OC* oral contraceptive, *PID* pelvic inflammatory disease

[a]Include asthma, emphysema, bronchitis

[b]Include angina, congestive heart failure, coronary artery disease

[c]Surgery completed > 1 year before ovarian cancer diagnosis or interview for indications other than ovarian cancer

[d]Diagnosis made > 1 year before ovarian cancer diagnosis or interview

[e]Include mixed, NOS, other invasive epithelial ovarian carcinoma, borderline serous

Table 2 Crude and adjusted odds ratios for the association between epithelial ovarian cancer and benign gynecologic conditions by type and number of condition

Gynecologic conditions	Cases (%)	Control (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI
Type of gynecologic conditions						
Endometriosis						
No	551 (91.8)	719 (95.6)	1.00	Referent	1.00	Referent
Yes	49 (8.2)	33 (4.4)	1.94	1.23–3.05	1.78	1.09–2.90
PID						
No	556 (92.7)	717 (95.4)	1.00	Referent	1.00	Referent
Yes	44 (7.3)	35 (4.7)	1.62	1.03–2.56	1.33	0.82–2.16
Fibroid						
No	350 (58.3)	477 (63.4)	1.00	Referent	1.00	Referent
Yes	250 (41.7)	275 (36.6)	1.24	0.99–1.54	1.10	0.86–1.40
Ovarian cyst						
No	520 (86.7)	668 (88.8)	1.00	Referent	1.00	Referent
Yes	80 (13.3)	84 (11.2)	1.22	0.88–1.70	1.18	0.83–1.69
# of gynecologic conditions						
0	294 (49.0)	420 (55.9)	1.00	Referent	1.00	Referent
1	214 (35.7)	255 (33.9)	1.20	0.95–1.52	1.18	0.92–1.52
2+	92 (15.3)	77 (10.2)	1.71	1.22–2.39	1.66	1.16–2.38
			p trend = 0.002		p trend = 0.006	

Diagnosis made > 1 year before ovarian cancer diagnosis or interview

OR odds ratio, *CI* confidence interval, *PID* pelvic inflammatory disease, # number

[a]Fully adjusted model—adjusted for age at diagnosis (cases)/interview (control), study site, marital status, education, BMI, parity, tubal ligation, duration of oral contraceptive use, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst. OR for # of gynecologic conditions not adjusted for endometriosis, fibroid, PID, ovarian cyst

Table 3 Crude and adjusted odds ratios for the association between epithelial ovarian cancer and benign gynecologic conditions stratified by histologic subtypes (serous vs. non-serous)

Benign gynecologic condition	Histologic subtype	Cases (%)	Adjusted OR[a]	95% CI
Endometriosis				
No	Serous	362 (94.3)	1.00	Referent
Yes		22 (5.7)	1.29	0.71–2.35
No	Non-serous	169 (86.2)	1.00	Referent
Yes		27 (13.8)	2.80	1.53–5.10
PID				
No	Serous	351 (91.4)	1.00	Referent
Yes		33 (8.6)	1.65	0.98–2.79
No	Non-serous	185 (94.4)	1.00	Referent
Yes		11 (5.6)	0.90	0.42–1.91
Fibroid				
No	Serous	228 (59.4)	1.00	Referent
Yes		156 (40.6)	1.08	0.82–1.43
No	Non-serous	109 (55.6)	1.00	Referent
Yes		87 (44.4)	1.22	0.85–1.75
Ovarian cyst				
No	Serous	335 (87.2)	1.00	Referent
Yes		49 (12.8)	1.16	0.76–1.75
No	Non-serous	167 (85.2)	1.00	Referent
Yes		29 (14.8)	1.13	0.68–1.90
# of gynecologic conditions				
0	Serous	192 (50.0)	1.00	Referent
1		138 (35.9)	1.18	0.89–1.57
2+		54 (14.1)	1.51	1.00-2.29
			p trend = 0.044	
0	Non-serous	91 (46.4)	1.00	Referent
1		67 (34.2)	1.20	0.82–1.75
2+		38 (19.4)	2.13	1.32–3.46
			p trend = 0.004	

Diagnosis made > 1 year before ovarian cancer diagnosis or interview

OR odds ratio, *CI* confidence interval, *PID* pelvic inflammatory disease

[a]Fully adjusted model—adjusted for age at diagnosis (cases)/interview (control), study site, marital status, education, BMI, parity, tubal ligation, duration of oral contraceptive use, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst. OR for # of gynecologic conditions not adjusted for endometriosis, fibroid, PID, ovarian cyst

and endometrioid (OR 5.17; 95% CI 2.30–11.64) and ovarian cysts with mucinous subtype (OR 3.35; 95% CI 1.33–8.44) (Table S1).

In analyses stratified by history of OC use, there was no consistent pattern or evidence of strong effect modification by OC use on the association between benign gynecologic conditions and ovarian cancer risk (Table 4). The association between endometriosis and ovarian cancer was more pronounced among OC ever- vs. never-users (OR 1.92; 95% CI 1.13–3.24 vs. OR 1.44; 95% CI 0.34–6.31). However, for PID, fibroid, ovarian cyst, and a history of 2 or more benign conditions, the trend was reversed. Test of interaction was not significant for any gynecologic condition.

Discussion

In this analysis of a large, population-based case–control study of African-American women, a history of at least one benign gynecologic condition was reported by approximately half of cases and controls. We observed a consistent association between a history of endometriosis and epithelial ovarian cancer. A consistently positive but non-significant association was observed with PID, while no apparent association was observed with fibroid or ovarian cyst. Having multiple conditions consistently showed a trend towards increased risk of ovarian cancer across histologic subtypes.

Table 4 Crude and adjusted odds ratios for the association between epithelial ovarian cancer and benign gynecologic conditions stratified by oral contraceptive use

Benign gynecologic condition	Oral contraceptive use	Cases (%)	Control (%)	Adjusted OR[a]	95% CI	$p_{interaction}$
Endometriosis						0.450
No	OC never use	180 (95.7)	155 (98.1)	1.00	Referent	
Yes		8 (4.3)	3 (1.9)	1.45	0.34–6.31	
No	OC ever use	371 (90.0)	564 (95.0)	1.00	Referent	
Yes		41 (10.0)	30 (5.1)	1.92	1.13–3.24	
PID						0.197
No	OC never use	176 (93.6)	153 (96.8)	1.00	Referent	
Yes		12 (6.4)	5 (3.2)	1.87	0.59–5.95	
No	OC ever use	380 (92.2)	564 (95.0)	1.00	Referent	
Yes		32 (7.8)	30 (5.1)	1.31	0.76–2.26	
Fibroid						0.703
No	OC never use	118 (62.8)	116 (73.4)	1.00	Referent	
Yes		70 (37.2)	42 (26.6)	1.23	0.73–2.06	
No	OC ever use	232 (56.3)	361 (60.8)	1.00	Referent	
Yes		180 (43.7)	233 (39.2)	1.06	0.80–1.40	
Ovarian cyst						0.127
No	OC never use	160 (85.1)	146 (92.4)	1.00	Referent	
Yes		28 (14.9)	12 (7.6)	1.88	0.84–4.20	
No	OC ever use	360 (87.4)	522 (87.9)	1.00	Referent	
Yes		52 (12.6)	72 (12.1)	1.00	0.66–1.51	
# of gynecologic conditions						0.483
0	OC never use	104 (55.3)	108 (68.4)	1.00	Referent	
1		57 (30.3)	39 (24.7)	1.38	0.81–2.33	
2+		27 (14.4)	11 (7.0)	2.36	1.07–5.19	
				p trend = 0.024		
0	OC ever use	190 (46.1)	312 (52.5)	1.00	Referent	
1		157 (38.1)	216 (36.4)	1.12	0.84–1.50	
2+		65 (15.8)	66 (11.1)	1.53	1.01–2.30	
				p trend = 0.055		

Diagnosis made > 1 year before ovarian cancer diagnosis or interview

OR odds ratio, *CI* confidence interval, *dz.* disease, *PID* pelvic inflammatory disease

[a]Fully adjusted model—adjusted for age at diagnosis (cases)/interview (control), study site, marital status, education, BMI, parity, tubal ligation, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst. OR for # of gynecologic conditions not adjusted for endometriosis, fibroid, PID, ovarian cyst

The most consistent association in our study was observed in women with a history of endometriosis, with increased risk seen across multiple analyses despite the relatively small number of women with the condition. Positive associations between endometriosis and clear cell and endometrioid subtypes confirm findings previously reported in population-based studies of primarily white women [1–4]. The risk of ovarian cancer in women with endometriosis may vary depending on diagnostic criteria used (clinical only vs. surgical-pathological confirmation), but approximate two-fold increased risk observed in our study is consistent with findings from the majority of studies examining women with self-reported history of endometriosis (OR 1.3–1.9) [1, 4, 23–26]. Women with a history of endometriosis also had higher odds of being diagnosed with serous ovarian cancer, but the association was not significant. Association between endometriosis and serous ovarian cancer has not been established in existing studies. A recent pooled analysis by Pearce et al. was the first to separately examine the association with high- vs. low-grade serous ovarian cancer and to report a positive association with only low-grade serous subtype [1]. Small sample size in our study precluded further stratification by tumor grade.

Despite the well-established epidemiologic linkage, underlying biological mechanisms driving the association between endometriosis and non-serous ovarian cancer remain to be fully elucidated. Histologically, increased rates of severe atypia with or without complex hyperplasia has

been observed in endometriotic implants adjacent to ovarian carcinoma [2, 6]. This suggests a possible multi-step transformation from benign endometriotic cells to carcinoma aided by the pro-inflammatory microenvironment, altered immune response, and hormonal imbalance. Molecular and genetic studies examining the association between endometriosis and ovarian cancer support the association [7].

We consistently observed an approximate 1.5-fold (up to 1.8-fold among OC never users) increase in ovarian cancer risk among women with a history of PID suggesting a modest association. Observed associations were not consistently significant, but this may be attributed to limitations in sample size and smaller effect size. A small number of case–control and cohort studies have found a 1.5- to twofold increased risk of ovarian cancer in women with a history of PID [9–11], but other studies have reported conflicting results [4, 13, 14]. A recent large pooled analysis of 13 population-based case–control studies found no association between PID and overall ovarian cancer risk, but reported increased risks of low-grade serous and endometrioid subtypes [23]. In our histologic subtype analyses, we observed a positive association with clear cell subtype, but not with endometrioid subtype. Possible linkage with low-grade serous, endometrioid and clear cell subtypes may suggest a shared pro-inflammatory pathway with endometriosis. Supplemental histologic subtype analysis was limited in sample size and exploratory in nature. These results must be interpreted with caution and await further confirmation.

We did not find associations between overall ovarian cancer and a history of fibroid or ovarian cyst, but increasing number of gynecologic conditions was consistently associated with increased risk of ovarian cancer, including both serous and non-serous subtypes. The risk associated with serous ovarian cancer in women with a history of multiple conditions was higher than individual associations observed in any one gynecologic condition. This observation may suggest a possible additive or synergistic effect on tumorigenesis influenced by the pro-inflammatory milieu from an increased burden in the number of benign conditions. Increased risk of serous ovarian cancer in women with other pro-inflammatory risk factors has been reported, most notably in talc users [4, 24].

Direction and magnitude of association and underlying biological mechanism contributing to ovarian cancer tumorigenesis are likely to vary by type of ovarian cyst pathology. Ovarian cyst can represent a wide range of pathologies from functional cysts to benign tumors to endometriomas, which are a type of endometriosis. Existing results vary widely from minimal to no ovarian cancer risk associated with symptomatic functional or stable simple ovarian cyst to twofold or greater increased risk if concomitant infertility or endometrioma is present [15, 16, 25, 26]. An association between ovarian cyst and mucinous ovarian cancer was observed in our histologic subtype analysis. The association between a history of ovarian cyst and mucinous ovarian cancer has not been previously reported, but the linkage is biologically plausible. Positive associations between self-reported history of ovarian cyst and mucinous borderline tumor, believed to be a precursor of invasive mucinous carcinoma, have been reported [12, 16]. More studies are needed to identify the epidemiologic risk factors for mucinous carcinoma, which appear to have molecular and genetic underpinnings distinct from other non-serous subtypes.

Overall, a history of OC use was common among both cases and controls, especially among women with gynecologic conditions. The well-established protective effect of OC has been hypothesized to be mediated by ovulation suppression, reduction in gonadotropins, and increase in apoptosis induced by increased progestin level [27, 28]. In the presence of gynecologic disease, OC may further help modulate ovarian cancer development by preventing hormonal stimulation of endometriotic cells, fibroid, and ovarian cyst and reducing the risk of recurrent PID. We explored the effect of OC use on gynecologic condition-related ovarian cancer risk in a stratified analysis. Overall, OC use did not appear to have a strong or consistent influence on the pattern of associations between benign gynecologic conditions and ovarian cancer beyond the known general protective effect.

This study has limitations that should be considered when interpreting the findings. The prevalence of the gynecologic conditions was based on unverified self-report and subject to misclassification and recall bias. The misclassification may be compounded by the relatively subjective nature of endometriosis or PID diagnosis. Additionally, endometrioma represents a type of ovarian cyst arising from endometriosis and may be reported as a history of ovarian cyst alone. As we do not have information on the type of ovarian cyst in our study, we are not able to estimate the prevalence of this misclassification. To reduce the potential surveillance bias, gynecologic conditions diagnosed within 1 year before ovarian cancer diagnosis or interview date were recoded as not having the condition. We cannot exclude the possibility of bias related to increased intensity and duration of surveillance for more severe disease; however, cases were less likely to have had a health check-up within 2 years and a sensitivity analysis censoring gynecologic diagnosis to 3, 5, or 10 years before ovarian cancer diagnosis demonstrated consistent associations. We also acknowledge that bias due to confounding by treatment of gynecologic conditions other than OC may exist. In our study, hysterectomy was not associated with ovarian cancer, nor did it appear to modify the association between benign gynecologic condition and ovarian cancer. The rate of unilateral oophorectomy among women with ovarian cysts was higher among controls (14 of 84) compared to cases (6 of 85), but small numbers did not allow subgroup analysis.

Our results represent findings from the largest case–control study of African-American women with ovarian cancer in the U.S. to date. Moreover, unlike reports from secondary analysis of other studies, AACES was specifically designed to investigate risk factors associated with ovarian cancer in African-American women. The large number of participants in our study allowed examination of associations between several common gynecologic conditions and ovarian cancer while adjusting for multiple confounders and known risk factors. In particular, talc powder use is highly prevalent in the African-American community and has been found to be associated with increased risk of ovarian cancer in this and other studies [4, 24, 29]. Indeed, regression models excluding talc use over-estimated the associations in our analyses.

In summary, we report positive associations between a self-reported history of endometriosis, and to a lesser degree PID, with ovarian cancer risk in African-American women similar to existing reports among non-African-American populations. Having more than one benign gynecologic condition also increased ovarian cancer risk.

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Compliance with ethical standards

Ethics approval and consent to participate The study protocol and questionnaire were approved by the Institutional Review Boards at Duke University Medical Center, Baylor College of Medicine, Case Western Reserve University School of Medicine, Louisiana State University, Robert Wood Johnson Medical School/Rutgers Cancer Institute, Wayne State University, the University of Alabama-Birmingham, the Medical University of South Carolina, and the University of Tennessee-Knoxville. Additionally, the protocol was approved by central cancer registries in the states of Alabama, Georgia, North Carolina, South Carolina, Tennessee, and Texas, SEER registries in New Jersey, Louisiana, and the Detroit metropolitan area, and 9 individual hospital systems in Ohio. All study participants completed informed consent prior to enrollment.

Availability of data and materials The dataset used and analyzed in this study is available after review from the AACES study investigators and with proper IRB approvals.

Conflict of interest The authors declare that they have no competing interests.

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